



Our STN: BL 125722/0

ACCELERATED BLA APPROVAL

November 13, 2024

PTC Therapeutics, Inc.
Attention: Agnes Cobbum, MS
100 Corporate Court
South Plainfield, NJ 07080

Dear Agnes Cobbum:

Please refer to your Biologics License Application (BLA) received March 15, 2024, submitted under section 351(a) of the Public Health Service Act (PHS Act) for eladocogene exuparvovec-tneq.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2168 to PTC Therapeutics, Inc., South Plainfield, NJ, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products and pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and the regulations for accelerated approval, 21 CFR 601.41. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license you are authorized to manufacture the product eladocogene exuparvovec-tneq, which is indicated for the treatment of adult and pediatric patients with aromatic L-amino acid decarboxylase (AADC) deficiency.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: 04903288, 01395641, and 02926066.

ACCELERATED APPROVAL REQUIREMENTS

Under accelerated approval statutory provisions and regulations we may grant marketing approval for a biological product on the basis of adequate and well-controlled studies establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. This approval requires you to study the biological product further, to verify and describe its clinical benefit, where there is

uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.

Approval under these statutory provisions and regulations requires, among other things, that you conduct adequate and well-controlled studies to verify and describe clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as improvement in clinical manifestations of AADC deficiency.

Accelerated Approval Required Studies

We remind you of your agreement to the postmarketing requirement specified in our e-mail communication of November 12, 2024.

1. Submit the clinical reports and datasets of clinical studies conducted in patients with AADC deficiency in the United States treated with eladocagene exuparvovec-tneq to verify and describe its clinical benefit. Such studies should, at minimum, evaluate the product's effects on the serious manifestations of AADC deficiency in adult and pediatric patients, including but not limited to motor function.

Draft Protocol: June 30, 2025

Final Protocol: December 31, 2025

Interim Report: December 31, 2026

Interim Report: December 31, 2027

Trial Completion: December 31, 2028

Final Report: September 30, 2029

We expect you to complete design, initiation, accrual, completion, and reporting of these studies within the framework described in our communication of November 12, 2024.

Please submit the protocols to your IND 19653, with a cross-reference letter to this BLA, STN BL 125722 explaining that these protocols were submitted to the IND. Please refer to the sequential number for each study and the submission number as shown in this letter.

You must conduct these studies with due diligence. If required postmarketing studies fail to verify that clinical benefit is conferred by eladocagene exuparvovec-tneq, or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval.

You must submit reports of the progress of each study listed above as required under section 506(c) of the FDCA to this BLA 180 days after the date of approval of this BLA and approximately every 180 days thereafter (see section 506B(a)(2) of the FDCA (hereinafter "180-day reports").

You are required to submit two 180-day reports per year for each open study or clinical trial required under 506(c) of the FDCA. The initial report will be a standalone submission and the subsequent report will be combined with your application's annual status report required under section 506B(a)(1) of the FDCA and 21 CFR 601.70. The standalone 180-day report will be due 180 days after the date of approval (with a 60-day grace period). Submit the subsequent 180-day report with your application's annual status report. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted.

Your 180-day report must include the information listed in 21 CFR 601.70(b). FDA recommends that you use form FDA 3989 PMR/PMC Annual Status Report for Drugs and Biologics, to submit your 180-day reports. Form FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at <https://www.fda.gov/about-fda/reports-manuals-forms/forms>.

Your 180-day reports, including both the standalone 180-day report submitted 180 days after the date of approval and the 180-day report submitted with your annual status report, must be clearly designated as **180-Day AA PMR Progress Report**.

FDA will consider the submission of your annual status report under section 506B(a)(1) of the FDCA and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2) of the FDCA. You are also required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) of the FDCA until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.

Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Postmarketing Requirements and 506B Commitments are fulfilled or released.

Please submit final study reports as a supplement to this BLA, STN BL 125722. For administrative purposes, all submissions related to this postmarketing study requirement must be clearly designated as **“Subpart E Postmarketing Study Requirements.”**

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture eladocagene exuparvovec-tneq drug substance and drug product at (b) (4) and to perform the final drug product labeling and packaging at (b) (4)

You may label your product with the proprietary name KEBILIDI and market it in single-dose vials containing 0.5 mL extractable volume at a concentration of 5.6×10^{11} vector genomes (vg)/mL.

ADVISORY COMMITTEE

We did not refer your application to the Cellular, Tissue, and Gene Therapies Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues which would have benefitted from an advisory committee discussion.

DATING PERIOD

The dating period for eladocogene exuparvovec-tneq shall be 48 months from the date of manufacture when stored at $\leq -65^{\circ}\text{C}$. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency. The dating period for your drug substance shall be (b) (4) when stored at (b) (4)

FDA LOT RELEASE

Please submit protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on FORM FDA 3486 to the Director, Office of Compliance and Biologics Quality, electronically through the eBPDR web application or at the address below. Links for the instructions on completing the electronic form (eBPDR) may be found on CBER's web site at <https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations>.

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of eladocagene exuparvovec-tneq, or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including Package Insert submitted in your e-mail submission, dated November 13, 2024, and the draft carton and container labels submitted under amendment 61, dated October 29, 2024.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the Package Insert submitted on November 8, 2024. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

PACKAGE AND CONTAINER LABELS

Please electronically submit final printed package and container labels identical to the package and container labels submitted on October 29, 2024, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-certain-human-pharmaceutical-product-applications>.

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125722 at the time of use and include implementation information on Form FDA 356h.

PROMOTIONAL MATERIALS

Please note that the accelerated approval regulation concerning promotional materials (21 CFR 601.45) stipulates that all advertising and promotional labeling items that you wish to distribute in the first 120 days following approval, must have been received by FDA prior to the approval date. After approval, promotional items intended for

dissemination after the first 120 days following approval must be submitted to the FDA at least 30 days prior to the anticipated distribution date. Please submit draft materials with a cover letter noting that the items are for accelerated approval, and an accompanying FORM FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertisement and promotional labeling at the time of initial dissemination or publication, accompanied by FORM FDA 2253 (21 CFR 601.12(f)(4)).

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs* at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format—Postmarketing Safety Reports* at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports> and FDA's Adverse Event reporting System website at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm>. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm>.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher (PRV), as provided under section 529 of the FDCA. This PRV has been assigned a tracking number, PRV BLA 125722. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the PRV must notify FDA of its intent to submit an application with a PRV at least 90 days before submission of the application and must include the date the sponsor intends to submit the application. This notification should be prominently marked, **“Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher.”**
- This PRV may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the PRV may be transferred, but each person to whom the PRV is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this PRV, you should refer to this letter as an official record of the voucher. If the PRV is transferred, the sponsor to whom the PRV has been transferred should include a copy of this letter (which will be posted on our website as are all approval letters) and proof that the PRV was transferred.
- FDA may revoke the PRV if the rare pediatric disease product for which the PRV was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a PRV must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
 - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
 - the estimated demand in the U.S. for the product, and
 - the actual amount of product distributed in the U.S.

You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease PRV Program webpage available at

<https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/RarePediatricDiseasePriorityVoucherProgram/default.htm>.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitments as described in our correspondence of November 12, 2024, as outlined below:

2. PTC Therapeutics commits to reassessing the acceptance criteria for release testing of KEBILIDI drug substance and drug product based on manufacturing experience and revising the acceptance criteria, if appropriate. A final acceptance criteria reassessment report will be submitted as a “Postmarketing Study Commitment – Final Study Report” within 60 days after release (under either the European license or US license) of the 10th commercial batch.

Final Report Submission: May 31, 2028

3. PTC commits to reevaluating the in-process acceptance criterion for the (b) (4) (b) (4) assay. PTC will submit the test results and revise the acceptance limit with justification based on the data as a Postmarketing Study Commitment – Final Study Report within 60 days after the 10th commercial batch is released under either the European license or US license.

Final study report submission: May 31, 2028

4. PTC commits to reevaluating the in-process acceptance limit for (b) (4) (b) (4) based on data from commercial batches tested using the (b) (4) from (b) (4). PTC will submit the test results and revise the acceptance limit with justification based on the data as a Postmarketing Study Commitment – Final Study Report within 60 days after release (under either the European license or US license) of the 10th commercial batch tested using the (b) (4) from (b) (4).

Final study report submission: May 31, 2028

5. PTC commits to perform additional robustness assessments for the (b) (4) (b) (4) assay, including variations in the number of (b) (4) and (b) (4).

The final report will be submitted as a “Postmarketing Study Commitment – Final Study Report”.

Final study report submission: May 31, 2025

6. PTC commits to evaluating suitability with (b) (4) as environmental isolates post-BLA approval/PMC to provide additional assurance your sterility test method can detect this known environmental isolate in addition to the indicated USP microorganisms.

Final qualification suitability will be submitted to CBER in Annual Report on January 31, 2026.

7. PTC commits to re-assessing the accuracy, precision, and linearity of the (b) (4) assay to cover the range of (b) (4) and including at least (b) (4) or more data points for assessment of linearity. The updated assay validation report and the validation protocol will be submitted as a “Postmarketing Study Commitment – Final Study Report”.

Final study report submission: May 31, 2025

We request that you submit information concerning chemistry, manufacturing, and control postmarketing commitments and final reports to this BLA, STN BL 125722. Please refer to the sequential number for each commitment.

Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Correspondence Status Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a **Postmarketing Study Commitment – Correspondence Status Update**. The status report for each commitment should include:

- the sequential number for each study as shown in this letter;
- the submission number associated with this letter;
- describe what has been accomplished to fulfill the non-section 506B PMC; and,
- summarize any data collected or issues with fulfilling the non-section 506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Commitment – Final Study Report** or **Supplement contains Postmarketing Commitment Final Study Report**.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely,

Melissa Mendoza
Director
Office of Compliance
and Biologics Quality
Center for Biologics
Evaluation and Research

'Lola Fashoyin-Aje, MD, MPH
Director
Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics
Evaluation and Research